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Cerebral perfusion, oxygenation and metabolism during exercise in young and elderly individuals

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Key points

- The influence of normative ageing on cerebral perfusion, oxygenation and metabolism during exercise is not well known.
- This study assessed cerebral perfusion and concentration differences for oxygen, glucose and lactate across the brain, in young and elderly individuals at rest and during incremental exercise to exhaustion.
- We observed that during submaximal exercise (at matched relative intensities) and during maximal exercise, cerebral perfusion was reduced in older individuals compared with young individuals, while the cerebral metabolic rate for oxygen and uptake of glucose and lactate were similar.
- The results indicate that the age-related reduction in cerebral perfusion during exercise does not affect brain uptake of lactate and glucose.

Abstract We evaluated cerebral perfusion, oxygenation and metabolism in 11 young (22 ± 1 years) and nine older (66 ± 2 years) individuals at rest and during cycling exercise at low (25% W_{max}), moderate (50% W_{max}), high (75% W_{max}) and exhaustive (100% W_{max}) workloads. Mean middle cerebral artery blood velocity (MCA V_{mean}), mean arterial pressure (MAP), cardiac output (CO) and partial pressure of arterial carbon dioxide (P_{aCO_2}) were measured. Blood samples were obtained from the right internal jugular vein and brachial artery to determine concentration differences for oxygen (O_2), glucose and lactate across the brain. The molar ratio between cerebral uptake of O_2 *versus* carbohydrate (O_2–carbohydrate index; O_2/[glucose + 1/2 lactate]; OCI), the cerebral metabolic rate of O_2 ($CMRO_2$) and changes in mitochondrial O_2 tension (P_{mitoO_2}) were calculated. 100% W_{max} was ~33% lower in the older group. Exercise increased MAP and CO in both groups ($P < 0.05$ *vs.* rest), but at each intensity MAP was higher and CO lower in the older group ($P < 0.05$). MCA V_{mean}, P_{aCO_2} and cerebral vascular conductance index (MCA V_{mean}/MAP) were lower in the older group at each exercise intensity ($P < 0.05$). In contrast, young and older individuals exhibited similar increases in $CMRO_2$ (by ~30 μmol (100 g^{-1}) min^{-1}), and decreases in OCI (by ~1.5) and P_{mitoO_2} (by ~10 mmHg) during exercise at ≥75% W_{max}. Thus, despite the older group having reduced cerebral perfusion and maximal exercise

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capacity, cerebral oxygenation and uptake of lactate and glucose are similar during exercise in young and older individuals.

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Abbreviations CBF, cerebral blood flow; $CMRO_2$, cerebral metabolic rate for oxygen; CO, cardiac output; HR, heart rate; MAP, mean arterial pressure; MCA V_{mean}, middle cerebral artery mean blood velocity; OCI, oxygen-to-carbohydrate index; OGI, oxygen-to-glucose index; P_{aCO_2}, partial pressure of arterial carbon dioxide; P_{capO_2}, cerebral capillary oxygen tension; P_{mitoO_2}, mitochondrial oxygen tension; S_{capO_2}, cerebral capillary oxygen saturation; SV, stroke volume; VC, vascular conductance; W_{max}, maximal power achieved during the incremental exercise protocol.

Introduction

Cross-sectional and longitudinal studies indicate that normative ageing is associated with reductions in regional and global resting cerebral blood flow (CBF) (Kety, 1956; Rogers *et al.* 1990; Ajmani *et al.* 2000; Scheel *et al.* 2000; Beason-Held *et al.* 2007; Ainslie *et al.* 2008). Resting cerebral energy metabolism is also reportedly altered, such that cerebral oxygen (O_2) and glucose consumption are both reduced (Kety, 1956; Kuhl *et al.* 1982; Pantano *et al.* 1984; Yamaguchi *et al.* 1986; Leenders *et al.* 1990), although this has not been a universal finding (Duara *et al.* 1983; de Leon *et al.* 1984). Age-related deficits in the brain are likely to become more evident during physiological perturbation, but the influence of ageing on CBF, oxygenation and metabolism during exercise remains incompletely understood, although perturbations of cerebral oxygenation and metabolism have been reported to prevent full activation of exercising skeletal muscles (i.e. provoke central fatigue) (Nybo & Rasmussen, 2007; Rasmussen *et al.* 2010).

In young healthy individuals, increases in CBF and cerebral oxygenation during low to moderate intensity dynamic exercise are believed to be coupled to enhanced cerebral neuronal activity, although haemodynamic, endothelial, neurogenic and neurohumoral factors may also contribute (Ide & Secher, 2000; Secher *et al.* 2008). At higher intensities of exercise, CBF and cerebral oxygenation tend to plateau and even return to resting levels, in line with the hyperventilation-induced fall in arterial carbon dioxide tension (P_{aCO_2}) (Ide & Secher, 2000; Ogoh *et al.* 2005). Age-related impairments in regulation of the skeletal muscle vasculature have been reported both at rest and especially during exercise, partly due to exaggerated sympathetic vasoconstriction, endothelial dysfunction and attenuated metabolic vasodilatation (Dinenno & Joyner, 2006; Proctor & Parker, 2006; Schrage *et al.* 2007; Kirby *et al.* 2012; Phillips *et al.* 2012). Whether such age-related circulatory alterations are operant in the brain remains unclear, and studies that have examined whether age influences the CBF responses to exercise are equivocal (Heckmann *et al.* 2003; Fisher *et al.* 2008; Marsden *et al.* 2012; Murrell *et al.* 2012). Middle cerebral artery mean blood velocity (MCA V_{mean}) is reportedly similar in young (24 ± 3 years) and older individuals (57 ± 7 years) during low and moderate intensity exercise, although the cerebral vascular conductance (VC) index was reduced more in the older group (Fisher *et al.* 2008). However, in studies involving more elderly individuals a lower MCA V_{mean} during exercise is found and attributed to age-related alterations in neuronal activity and metabolism (Marsden *et al.* 2012), which may lead to inadequate cerebral oxygen provision.

At rest, the cerebral energy demand is provided almost exclusively by the oxidation of glucose, such that the molar ratio between the cerebral uptake of O_2 *versus* that of glucose (the O_2–glucose index; OGI) is ~6 (Seifert & Secher, 2011). The OGI decreases during augmented neuronal activation as the cerebral uptake of glucose increases more than that of O_2 (Fox *et al.* 1988). Along with glucose, lactate is also a substrate supporting cerebral metabolism. Although at rest a small amount of lactate is released by the brain, dynamic exercise evokes an intensity-dependent increase in cerebral uptake of lactate, and the combined uptake of lactate and glucose is in excess of the O_2 uptake (Seifert & Secher, 2011). Thus, the O_2–carbohydrate index (OCI), calculated as O_2/(glucose + 1/2 lactate), is reduced from 5.7 to < 2 during maximal whole body exercise (i.e. rowing) (Volianitis *et al.* 2008). This pronounced increase in cerebral lactate uptake is mainly governed passively by its availability, which is proportional to the exercise-induced increase in arterial lactate concentration (Ide *et al.* 1999; Quistorff *et al.* 2008; van Hall *et al.* 2009; Rasmussen *et al.* 2011), and has also been linked to a β_2-adrenergic mechanism (Larsen *et al.* 2008; Seifert *et al.* 2009*c*), the size of the active skeletal muscle mass (Dalsgaard *et al.* 2004), activation of central command (Dalsgaard *et al.* 2002) and sensory feedback from skeletal muscle afferents (Dalsgaard *et al.* 2003). Although not a universal finding (Volianitis *et al.* 2008), OCI has been reported to be reduced by inadequate CBF and cerebral oxygenation (Rasmussen *et al.* 2010; Overgaard *et al.* 2012). Therefore, in elderly individuals

with potentially impaired cerebral perfusion there could be a greater reduction in OCI during exercise. Conversely, age-related reductions in arterial lactate accumulation (Hagberg *et al.* 1988), sensory feedback from skeletal muscle afferents (Markel *et al.* 2003) and muscle mass (Doherty, 2003) could mean that there is a less pronounced reduction in OCI during exercise in elderly individuals.

The present study investigated cerebral perfusion, oxygenation and metabolism during exercise in aged humans. Cerebral perfusion was assessed using the transcranial Doppler technique, mean arterial pressure (MAP) measured, and a cerebral VC index calculated in young and elderly subjects at rest and during a discontinuous incremental exercise protocol to exhaustion. Given the inherent limitations associated with employing brain-imaging techniques during vigorous dynamic exercise, we used arterial to internal jugular venous differences to assess whole brain metabolism and oxygenation. We hypothesised that during exercise older individuals would exhibit lower cerebral perfusion and oxygenation, and a more pronounced reduction in OCI in comparison to their younger counterparts.

Methods

Eleven young (age 22 ± 1 years, weight 76 ± 2 kg, height 1.85 ± 0.02 m (±SEM)) and nine older individuals (age 66 ± 2 years, weight 86 ± 5 kg, height 1.82 ± 0.02 m) participated in the study. All experimental protocols and procedures conformed to the *Declaration of Helsinki* and were approved by the local ethics committee in Copenhagen (Protocol number H-1-2010-141). Prior to participation, a detailed verbal and written explanation of the study was provided, and written informed consent to take part obtained. No subject had a history or symptoms of cardiovascular, pulmonary, metabolic or neurological disease, and none was using prescribed or over-the-counter medications. All subjects were recreationally active, and no one was a competitive athlete or had experienced a recent prolonged period of physical inactivity (e.g. bed rest). Prior to experimental sessions subjects were requested to abstain from strenuous physical activity and alcohol for at least 24 h, caffeinated beverages for 12 h and food for 2 h. Studies were performed with external stimuli minimised and at an ambient room temperature of 23–24°C.

Experimental protocol

Subjects performed a discontinuous incremental maximal exercise protocol on a cycle ergometer (Ergomedic 874E; Monarch, Stockholm, Sweden). Subjects sat quietly on the ergometer for a 5 min baseline period prior to the first workload. Each exercise workload lasted 5 min, and was separated by 5 min of recovery. During recovery periods subjects pedalled backwards to obviate the development of a vasovagal syncope. Subjects maintained a pedal frequency of 60 r.p.m. at each workload. The exercise workload commenced at 60 W and was increased stepwise by 30 W until exhaustion, defined as when the subjects were unable to maintain 60 r.p.m. despite verbal encouragement. The maximal power achieved during the incremental exercise protocol was defined as 100% W_{max}. Blood samples were obtained simultaneously from the brachial artery and the internal jugular vein during the final minute of each experimental phase. Rating of perceived exertion (RPE) was expressed using the 6–20 scale at the end of each workload (Borg, 1982).

Experimental measures

With the subject placed slightly head-down on a hospital bed, guided by ultrasound, a catheter (1.6 mm; 14 gauge; ES-04706, Arrow International, Reading, PA, USA) was inserted under local anaesthesia (lidocaine, 2%) retrograde in the right internal jugular vein, and the catheter tip advanced to the bulb of the vein. Blood sampled from this site was considered to represent the outlet of the brain, although the potential for a small contribution from cerebrospinal fluid drained through the sinus sagittalis is recognised. A second catheter (1.1 mm ID, 20 gauge) was placed in the brachial or radial artery of the non-dominant arm for blood sampling and MAP measurement. This was connected to a pressure transducer (Baxter, Uden, the Netherlands), zeroed at the level of the right atrium, and interfaced with a Dialogue 2000 monitor (IBC-Danica, Copenhagen, Denmark). Subjects rested supine for 1 h after catheterization prior to the collection of any experimental data, to offset changes in cerebral metabolism caused by 'arousal' and nociceptive stimuli (Seifert *et al.* 2009*c*). Heart rate (HR) was monitored using a lead II electrocardiogram (ECG). Stroke volume (SV) was estimated offline using the Modelflow method (Beatscope; FMS, Amsterdam, The Netherlands), which simulates aortic flow waveforms from an arterial pressure signal using a non-linear three-element model of the aortic input impedance (Bogert & van Lieshout, 2005). Given their importance in determining the elastic properties of the aorta, height, weight, age and gender of the subject are used in calculations of aortic impedance and arterial compliance. Cardiac output (CO) was calculated as SV × HR, and systemic VC as CO/MAP. The Modelflow method has been shown to reliably estimate rapid changes in SV and CO during a variety of experimental protocols (Jellema *et al.* 1999; Pott *et al.* 2003), including dynamic exercise (Sugawara *et al.* 2003; Tam *et al.* 2004).

MCA V_{mean} was measured using transcranial Doppler ultrasonography (DWL, Sipplingen, Germany) with a 2 MHz probe placed over the temporal ultrasound

window. An optimal signal-to-noise ratio was obtained at a depth of 48–60 mm and the probe fixed with an adjustable headband. A cerebral VC index was calculated as MCA V_{mean}/MAP. ECG, arterial blood pressure and MCA V_{mean} signals were sampled at 1000 Hz, and stored for offline analysis (Chart v5.2 and Powerlab; ADInstruments, Bella Vista, NSW, Australia). MAP was obtained by integrating the arterial pressure waveform on a beat-to-beat basis. MAP, HR, CO, systemic VC, MCA V_{mean} and cerebral VC index were calculated, and averaged at rest and during the last 30 s of each workload.

Cerebral metabolism

Arterial and jugular venous blood samples were obtained simultaneously in heparinized syringes and immediately analysed for blood gas variables, glucose and lactate using an ABL 725 (Radiometer, Copenhagen, Denmark). Brain metabolism was evaluated using OCI (molar ratio between the O_2 and carbohydrate (glucose and lactate) taken up by the brain; OCI = O_2/(glucose + 1/2 lactate)) and OGI (molar ratio between the cerebral uptake of O_2 *versus* glucose; OGI = O_2/glucose). Pyruvate was not included in the calculations, despite being a viable source of carbohydrate, as its uptake is an order of magnitude lower than that of lactate (Rasmussen *et al.* 2006). The fractional extraction of oxygen, glucose and lactate was determined by dividing the arterial to jugular venous concentration difference by the arterial concentration (Seifert *et al.* 2009*a*). For technical reasons blood samples were not obtained in one young subject. In addition, jugular venous lactate was not obtained in one young subject at 100% W_{max}, and to retain statistical power missing data were substituted with the mean of the respective group (Donders *et al.* 2006).

Calculations

Capillary O_2 saturation (S_{capO_2}) was:

$$S_{cap}O_2 = \frac{S_aO_2 + S_vO_2}{2}$$

where S_{aO_2} is the arterial O_2 saturation and S_{vO_2} is the internal jugular venous O_2 saturation (Gjedde *et al.* 2005; Rasmussen *et al.* 2007). With the assumption that capillary recruitment is absent within the brain, cerebral capillary O_2 tension (P_{capO_2}) was calculated as:

$$P_{cap}\ O_2 = P_{50a}^{Hb} \sqrt[h_a]{\frac{S_{cap}}{1 - S_{cap}}}$$

where, P_{50a}^{Hb} is the P_{O_2} when haemoglobin is half saturated (26 mmHg) and h_a is the Hill coefficient for arterial blood (2.84). The fundamental assumption for this approach is that O_2 extraction rises in proportion to distance as the blood traverses the capillary network from arterial to venous end, because the capillary geometry is such that all segments of the capillary bed satisfy coequal amounts of brain tissue.

The cerebral metabolic rate for O_2 ($CMRO_2$) was determined from the arterial to jugular venous difference for O_2, multiplied by resting global CBF (estimated as 46 ml (100 g^{-1}) min^{-1}; Madsen *et al.* 1995) adjusted in proportion to exercise-induced changes in MCA V_{mean} and assuming a constant vessel diameter (Serrador *et al.* 2000). Given the likely age-related differences in CBF (Kety, 1956; Rogers *et al.* 1990; Ajmani *et al.* 2000; Scheel *et al.* 2000; Beason-Held *et al.* 2007; Ainslie *et al.* 2008), only changes in $CMRO_2$ relative to rest are presented (i.e. $\Delta CMRO_2$). Mitochondrial oxygen tension (P_{mitoO_2}) was calculated as:

$$P_{mito}O_2 = P_{cap}O_2 - \frac{CMRO_2}{L}$$

and changes relative to rest were calculated (i.e. ΔP_{mitoO_2}). O_2 diffusibility (L) was taken as 4.4 μmol (100 g^{-1}) min^{-1} mmHg^{-1} (Rasmussen *et al.* 2007).

Data analysis

As aerobic capacity decreases with age (Fleg *et al.* 1995), young and older subjects were compared at the same relative exercise intensities, representing low (25% W_{max}), moderate (50% W_{max}), high (75% W_{max}) and exhaustive (100% W_{max}) exercise workloads. Comparisons of variables were made using a two-way repeated-measures ANOVA, in which group (young *vs.* older) and experimental phase (rest, 25% W_{max}, 50% W_{max}, 75% W_{max}, 100% W_{max}) were the main factors. *Post hoc* analysis was employed using Student–Newman–Keuls test to evaluate main effects and interactions. Statistical significance was set at $P < 0.05$. Analyses were conducted using SigmaStat (Jandel Scientific Software, SPSS, Chicago, IL, USA) for Windows.

Results

Subject characteristics

The mean age difference between young and older subjects was 44 years, but there were no significant age-group differences in weight and height. The maximal workload (100% W_{max}) achieved was approximately 33% lower in the older group (273 ± 12 *vs.* 183 ± 16 W, young *vs.* old, $P < 0.05$). Thus, the absolute workload performed at each relative exercise intensity was lower in the older group (68 ± 4 *vs.* 50 ± 5, 139 ± 6 *vs.* 97 ± 10, and 205 ± 9 *vs.* 143 ± 11 W, in young and older groups, for the 25% W_{max}, 50% W_{max} and 75% W_{max} and exercise bouts, respectively).

Haemodynamics

Resting MAP was higher and systemic VC was lower in older subjects ($P < 0.05$), whereas HR and CO were similar between young and older groups ($P > 0.05$ Fig. 1). Exercise increased MAP, HR, CO and systemic VC in both groups of subjects ($P < 0.05$ *vs.* rest), but at each workload MAP was higher in the older group, whereas HR, CO and systemic VC were lower ($P < 0.05$).

MCA V_{mean} and the cerebral VC index were lower in older individuals at rest (MCA V_{mean} 61 ± 4 *vs.* 43 ± 2 cm s^{-1} in young and older groups, respectively; $P < 0.05$; Fig. 2) and at each exercise intensity remained lower in the older group ($P < 0.05$). MCA V_{mean} increased from rest to submaximal exercise (65 ± 4 *vs.* 46 ± 3 cm s^{-1} at 25% W_{max}, 69 ± 3 *vs.* 46 ± 3 cm s^{-1} at 50% W_{max} and 68 ± 4 *vs.* 45 ± 2 cm s^{-1} at 75% W_{max}; $P < 0.05$ rest *vs.* 25% W_{max}, 50% W_{max} and 75% W_{max}) and returned to baseline during maximal exercise in both groups (62 ± 4 *vs.* 41 ± 1 cm s^{-1} at 100% W_{max}). When considered as a percentage change from rest, similar changes in MCA V_{mean} were observed. Cerebral VC index increased from rest to exercise at 25% W_{max} and 50% W_{max} in the young group ($P < 0.05$ *vs.* rest), was unchanged from rest at 75% W_{max} and fell below resting levels during maximal exercise ($P < 0.05$). No change in the cerebral VC index was observed in the older group during submaximal exercise and during maximal exercise it fell below resting values ($P < 0.05$ rest *vs.* 100% W_{max}). These changes occurred on a background of a lower P_{aCO_2} in older individuals both at rest and during exercise ($P < 0.01$). In both groups, P_{aCO_2} was elevated above resting levels during exercise at 25% W_{max} and 50% W_{max} ($P \leq 0.05$), and fell below resting levels during exercise $\geq$75% W_{max} ($P < 0.05$). RPE was slightly but significantly higher in young subjects at each relative exercise intensity (10 ± 1 *vs.* 9 ± 1, 15 ± 0.4 *vs.* 13 ± 1, 18 ± 0.3 *vs.* 16 ± 0.3 and 20 ± 0.1 *vs.* 19 ± 0.4, in young and older groups, for 25% W_{max}, 50% W_{max}, 75% W_{max} and 100% W_{max}, respectively, $P < 0.05$).

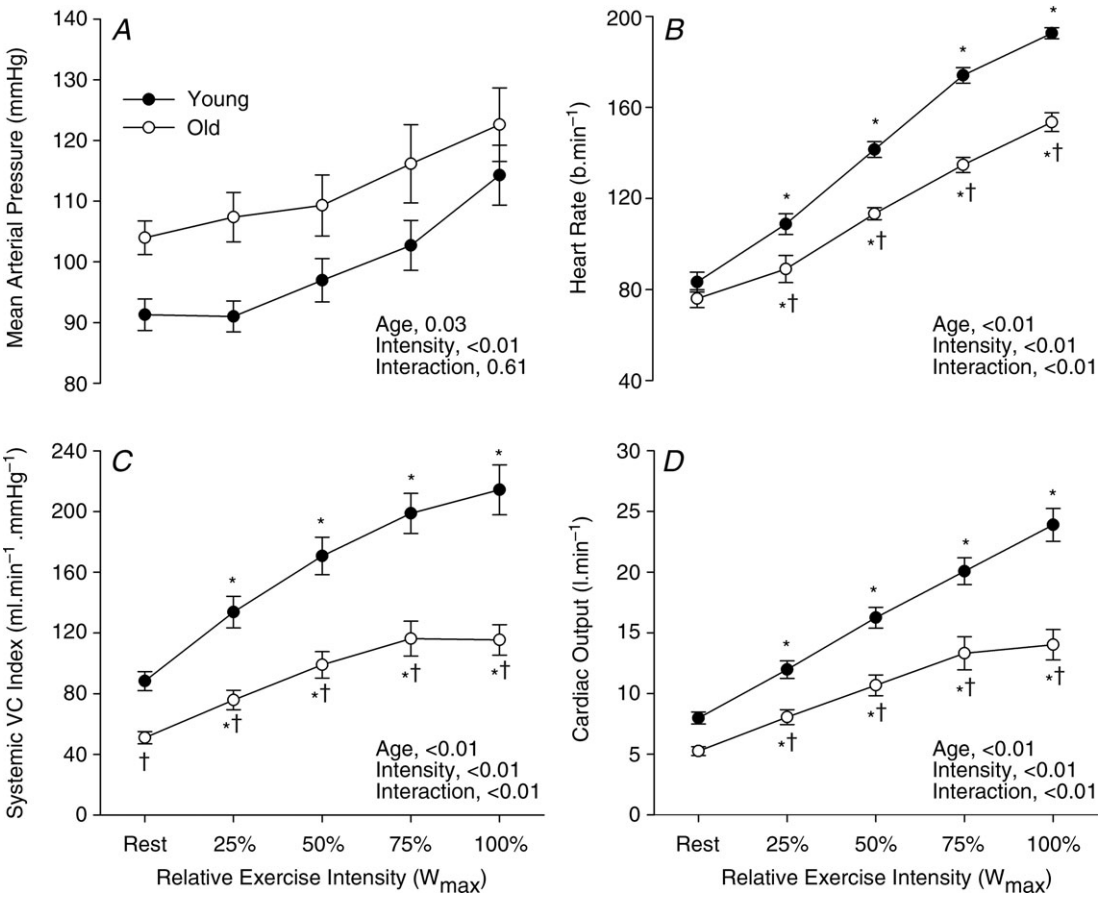

Figure 1. Mean arterial pressure, heart rate, systemic VC and cardiac output at rest and during submaximal and maximal exercise in young and older individuals
A, mean arterial pressure; *B*, heart rate; C, systemic VC; *D*, cardiac output. Young and older subjects are compared at the same relative exercise intensities, representing low (25% W_{max}), moderate (50% W_{max}), high (75% W_{max}) and exhaustive (100% W_{max}) exercise workloads. Systemic VC, systemic vascular conductance. Values are mean ± SEM. *P* values represent ANOVA results. *$P < 0.05$ *vs.* rest, †$P < 0.05$ *vs.* young.

Arterial oxygen, glucose and lactate concentrations

The arterial oxygen concentration was elevated during exercise in both groups of subjects, but was lower in the older group at rest and during the 75% and 100% W_{max} workloads ($P < 0.05$; Table 1). Arterial lactate increased from rest in both subject groups during high intensity exercise ($P < 0.05$ rest *vs.* 75% W_{max}, 100% W_{max}), although the increase was smaller in the older group at 100% W_{max} ($P < 0.05$). Arterial glucose concentrations were similar among groups and were not altered during exercise.

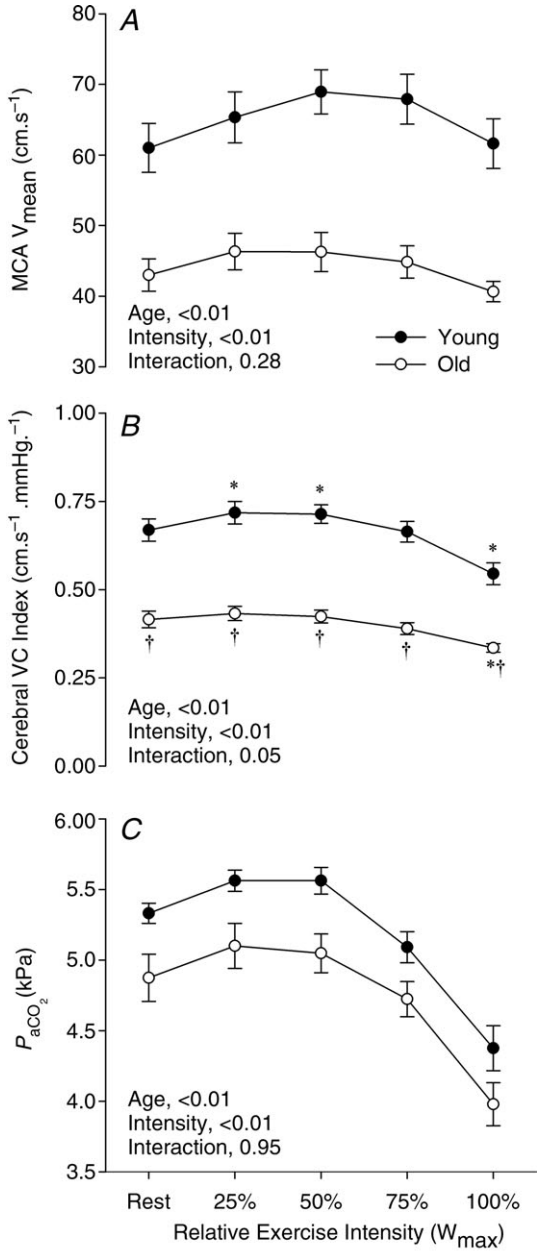

Figure 2. MCA V_{mean}, cerebral VC index and P_{aCO_2} at rest and during submaximal and maximal exercise in young and older individuals
A, MCA V_{mean}; *B*, cerebral VC index; *C*, P_{aCO_2}. V_{mean}, middle cerebral artery mean blood velocity; cerebral VC, cerebral vascular conductance; P_{aCO_2}, partial pressure of arterial carbon dioxide. Values are mean ± SEM. *P* values represent ANOVA results. *$P < 0.05$ *vs.* rest, †$P < 0.05$ *vs.* young.

Cerebral metabolism

At rest, net brain arterial–venous differences for O_2, lactate and glucose were similar in young and older groups (Table 1). The arterial–venous difference for O_2 was unaltered during submaximal exercise, but reduced from rest in both groups at 100% W_{max} ($P < 0.05$ *vs.* rest). The arterial–venous difference for lactate increased during exercise ($P < 0.05$ *vs.* rest at 75% and 100% W_{max}), with no significant effect of age. The arterial–venous difference for glucose remained unchanged from rest in both groups during exercise. Resting OGI and OCI were similar in young and older groups at rest. During exercise OCI was reduced from rest to the same extent in young and older groups ($P < 0.05$ *vs.* rest at 75% and 100% W_{max}), whereas OGI remained unchanged from rest at all exercise intensities (Fig. 3).

Cerebral oxygenation

Cerebral capillary oxygen saturation (S_{capO_2}) and partial pressure (P_{capO_2}) were similar in young and older subject groups, and were reduced from rest at 100% W_{max} ($P < 0.05$ *vs.* rest; Table 2). Exercise increased $\Delta CMRO_2$ at high and exhaustive exercise ($P < 0.05$ *vs.* rest at 75% and 100% W_{max}) to a similar extent in young and older groups. The magnitude of the reduction in ΔP_{mitoO_2} during exercise was similar in both groups ($P < 0.05$ *vs.* rest at 75% and 100% W_{max}, $P > 0.05$ young *vs.* older; Fig. 3).

Discussion

The major findings of the study are twofold. First, during exercise cerebral perfusion is reduced in older individuals compared with young individuals, while brain uptake of oxygen, glucose and lactate and reductions in OCI during exercise were similar in both groups. Second, increases in $\Delta CMRO_2$ and reductions in S_{capO_2}, P_{capO_2} and ΔP_{mitoO_2} are of a similar magnitude in young and older individuals during submaximal exercise at matched relative intensities and during maximal exercise. The similar reduction in cerebral capillary oxygenation and ΔP_{mitoO_2} at exhaustion (100% W_{max}), despite the absolute workloads undertaken being lower in the older group, may indicate a common central element to exercise capacity (i.e. fatigue).

Table 1. Arterial concentrations, arterial to internal jugular venous concentration differences (A–V diff) and the fractional extraction of O_2, glucose and lactate at rest and during submaximal and maximal exercise in young and older individuals

	Group	Rest	25% W_{max}	50% W_{max}	75% W_{max}	100% W_{max}	Age	*P* value intensity	Interaction
Arterial O_2 (mM)	Young	9.5 ± 0.2	9.5 ± 0.1	9.6 ± 0.2	9.9 ± 0.2*	10.1 ± 0.2*	0.02	<0.01	0.03
	Old	8.7 ± 0.2†	9.0 ± 0.2*	9.0 ± 0.2*	9.2 ± 0.2*†	9.4 ± 0.3*†			
Arterial lactate (mM)	Young	1.0 ± 0.1	1.1 ± 0.1	2.2 ± 0.2	6.0 ± 0.3*	13.7 ± 1.0*	0.03	<0.01	<0.01
	Old	0.9 ± 0.1	1.4 ± 0.2	2.2 ± 0.3	4.7 ± 0.6*	8.8 ± 1.1*†			
Arterial glucose (mM)	Young	5.9 ± 0.2	6.0 ± 0.2	6.0 ± 0.2	5.7 ± 0.2	5.9 ± 0.3	0.16	0.70	0.59
	Old	6.2 ± 0.1	6.2 ± 0.2	6.2 ± 0.2	6.3 ± 0.2	6.4 ± 0.3			
A–V diff O_2 (mM)	Young	3.3 ± 0.2	3.0 ± 0.1	3.0 ± 0.1	3.3 ± 0.1	3.9 ± 0.2	0.64	<0.01	0.64
	Old	3.2 ± 0.2	3.3 ± 0.3	3.1 ± 0.3	3.5 ± 0.2	4.0 ± 0.2			
A–V diff lactate (mM)	Young	−0.05 ± 0.02	0.00 ± 0.00	0.03 ± 0.02	0.35 ± 0.06	1.16 ± 0.30	0.91	<0.01	0.15
	Old	0.01 ± 0.03	0.09 ± 0.03	0.16 ± 0.05	0.41 ± 010	0.77 ± 0.24			
A–V diff glucose (mM)	Young	0.7 ± 0.0	0.6 ± 0.0	0.5 ± 0.0	0.6 ± 0.0	0.6 ± 0.0	0.19	0.74	0.28
	Old	0.6 ± 0.1	0.7 ± 0.1	0.7 ± 0.1	0.7 ± 0.1	0.7 ± 0.1			
E_{oxygen} (%)	Young	34 ± 1	32 ± 1	31 ± 1	34 ± 1	38 ± 2	0.17	<0.01	0.78
	Old	37 ± 2	37 ± 2	35 ± 3	39 ± 3	43 ± 3			
$E_{lactate}$ (%)	Young	−6 ± 3	0 ± 0	1 ± 1	6 ± 1	8 ± 2	0.53	0.77	0.27
	Old	0 ± 3	7 ± 2	6 ± 2	8 ± 1	8 ± 2			
$E_{glucose}$ (%)	Young	11 ± 0.4	10 ± 0.3	8 ± 1	10 ± 1	10 ± 1	<0.01	<0.01	0.35
	Old	10 ± 1	11 ± 2	11 ± 1	11 ± 1	11 ± 2			

Values are mean ± SEM. *P* values represent ANOVA results. *$P < 0.05$ *vs.* rest, †$P < 0.05$ *vs.* young. Young and older subjects are compared at rest, and at the same 'relative' exercise intensities, representing low (25% W_{max}), moderate (50% W_{max}), high (75% W_{max}) and exhaustive (100% W_{max}) exercise workloads. E_{oxygen}, fractional extraction of oxygen; $E_{lactate}$, fractional extraction of lactate; $E_{glucose}$, fractional extraction of glucose.

Cerebral perfusion, age and exercise

The observed age-related attenuation in cerebral perfusion at rest is in line with assessments in populations of a similar age using transcranial Doppler ultrasonography (Ainslie *et al.* 2008; Murrell *et al.* 2012), the Kety Schmidt technique (Kety, 1956), positron emission tomography (Leenders *et al.* 1990; Beason-Held *et al.* 2007) and colour Duplex sonography (Scheel *et al.* 2000). Although not assessed in the present investigation, such age-related reductions in cerebral perfusion may reflect global brain atrophy (Raz *et al.* 2000) and/or reduced neuronal activity (Rogers *et al.* 1990; Martin *et al.* 1991). During submaximal exercise (25–75% W_{max}) cerebral perfusion increased from resting levels in both young and older subject groups, but remained lower in the older group, in agreement with reports examining populations of a similar age (Marsden *et al.* 2012; Murrell *et al.* 2012). In addition, we observed that the increase in cerebral VC index in young individuals during low to moderate intensity exercise (25% and 50% W_{max}) was absent in the older individuals. Providing a mechanistic explanation for the lower cerebral perfusion and reduced cerebral vasodilatory response to exercise in older individuals is challenging. However, it is likely that the reduced cerebral VC index response is an expression of an age-associated blunting of regional blood flow in the resting state and in response to exercise. Alternatively, it could be considered an adaptive response to offset the age-related exaggerated increase in blood pressure (Fisher *et al.* 2008; Marsden *et al.* 2012), an attenuation of the exercise-induced increase in CO (Hagberg *et al.* 1985), an enhanced activation of cerebrovascular sympathetic nerve activity (Mitchell *et al.* 2009) or an impairment in endothelial and metabolic vasodilatation (Mayhan *et al.* 2008). In confirmation of observations by others (Marsden *et al.* 2012), we observed that P_{aCO_2} was lower in the older individuals both at rest and during exercise. Given the cerebral vasodilatory actions of CO_2, it is likely that the lower P_{aCO_2} in the elderly individuals contributed to the blunted cerebral VC index response observed in this group.

Cerebral metabolism, age and exercise

At rest, the arterial to jugular venous concentration differences and fractional extraction of O_2, lactate and glucose were similar in young and older individuals, suggesting that normative ageing does not influence the cerebral uptake of these molecules. In addition, the molar ratio between the cerebral uptake of O_2 *versus* that of glucose (OGI), and molar ratio between the cerebral uptake of O_2 *versus* that of carbohydrate ($OCI = O_2/\text{glucose} + \frac{1}{2}\,\text{lactate}$) were not significantly different in young and older individuals. In young individuals undertaking low to moderate intensity exercise

OCI is relatively stable (at ∼5.7). However, OCI is markedly reduced from resting levels during high to maximal intensity whole-body exercise (∼3–4), as the cerebral uptake of carbohydrate (in particular lactate) increases to a greater extent than the increase in O_2. In the present investigation, remarkably similar reductions in OCI were observed in young and older groups during strenuous exercise (≥75% W_{max}). The mechanism(s) for such exercise induced increases in brain lactate uptake and reduction in OCI remains incompletely understood. Several factors have been implicated, including an exercise-induced increase in arterial lactate concentration (Ide *et al.* 1999; Quistorff *et al.* 2008) and especially so during hypoxia (Rasmussen *et al.* 2010). A β_2-adrenergic mechanism may also be important in the exercise-induced increase in cerebral glucose and oxygen uptake and a reduction in OCI, although whether a β_2-adrenergic mechanism facilitates an increase in cerebral uptake of lactate independently of a change in arterial lactate concentration remains unclear (Larsen *et al.* 2008; Seifert *et al.* 2009*c*). On the basis of the findings of the present study we can conclude only that the brain maintains its ability to take up lactate and glucose during exercise in healthy ageing. Additional studies are required to elucidate the influence of age on cerebral lactate turnover, uptake and release, during exercise (i.e. via a tracer dilution method), and the potential involvement of a β_2-adrenergic mechanism (e.g. pharmacological intervention, catecholamine measurement).

Cerebral oxygenation, age and exercise

Along with supply of carbohydrate, the brain requires provision of O_2. Cerebral oxygenation was evaluated by estimates of S_{capO_2}, P_{capO_2} and P_{mitoO_2} (Gjedde *et al.* 2005; Rasmussen *et al.* 2007; Seifert *et al.* 2009*b*). In young healthy individuals cerebral oxygenation is somewhat elevated during low to moderate exercise intensities, but decreases during vigorous to maximal exercise (Seifert *et al.* 2009*b*) to the extent that it could

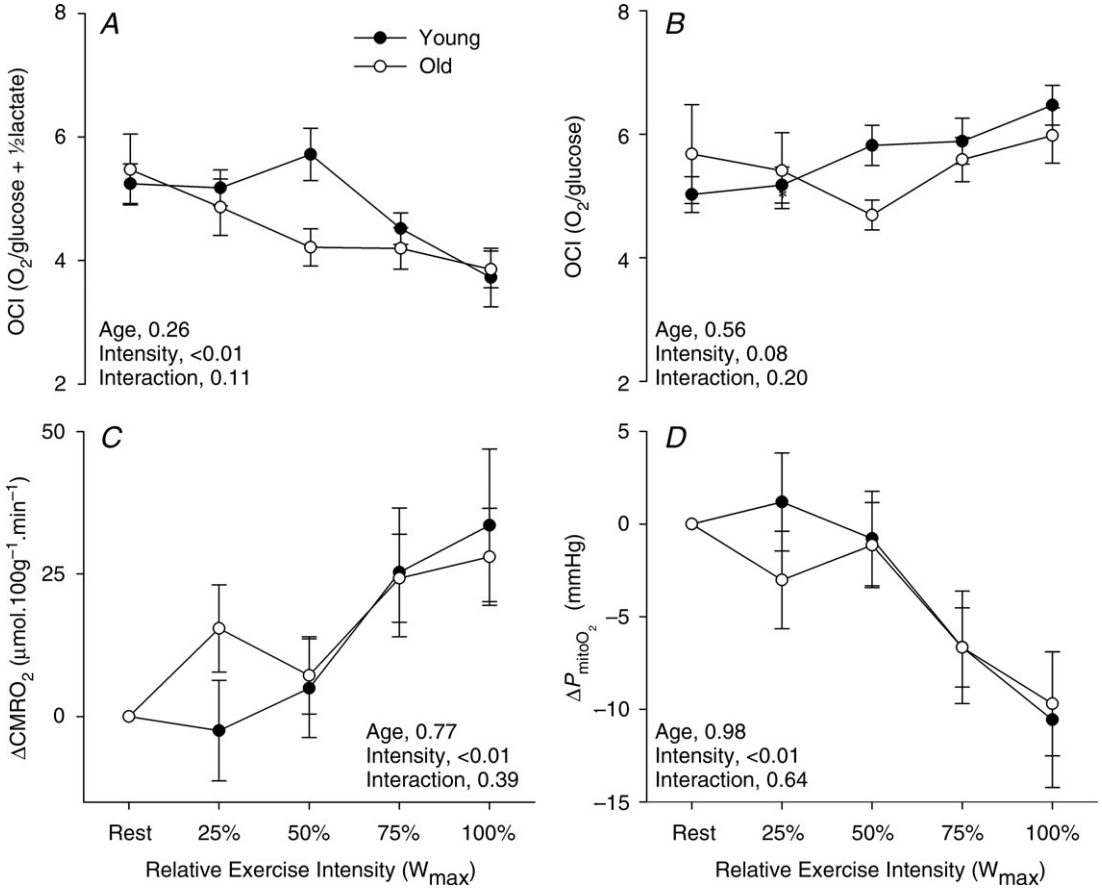

Figure 3. OCI, OGI, $\Delta CMRO_2$ and ΔP_{mitoO_2} at rest and during submaximal and maximal exercise in young and older individuals
A, OCI; *B*, OGI; *C*, $\Delta CMRO_2$; *D*, ΔP_{mitoO_2}. OCI represents the molar ratio between the O_2 and carbohydrate (glucose and lactate) taken up by the brain; OGI, molar ratio between the cerebral uptake of O_2 *versus* glucose; $\Delta CMRO_2$, change from rest in cerebral metabolic rate for O_2; ΔP_{mitoO_2}, change from rest in mitochondrial oxygen tension. Values are mean ± SEM. *P* values represent ANOVA results. $^*P < 0.05$ *vs.* rest, †$P < 0.05$ *vs.* young.

Table 2. Arterial pH, Hb concentration, P_{aCO_2}, P_{aO_2}, P_{vO_2}, S_{aO_2}, S_{vO_2} and brain capillary oxygen saturation (S_{capO_2}) and partial pressure (P_{capO_2}) at rest and during submaximal and maximal exercise in young and older individuals

	Group	Rest	25% W_{max}	50% W_{max}	75% W_{max}	100% W_{max}	Age	P value intensity	Interaction
Arterial pH	Young	7.42 ± 0.01	7.40 ± 0.01*	7.39 ± 0.01*	7.37 ± 0.01*	7.31 ± 0.01*	0.17	<0.01	<0.01
	Old	7.43 ± 0.01	7.40 ± 0.01*	7.40 ± 0.01*	7.38 ± 0.01*	7.36 ± 0.02*†			
Arterial Hb (mM)	Young	9.6 ± 0.2	9.7 ± 0.1*	9.9 ± 0.2*	10.1 ± 0.2*	10.5 ± 0.2*	0.01	<0.01	0.95
	Old	8.9 ± 0.2†	9.2 ± 0.2*	9.2 ± 0.2*†	9.4 ± 0.2*†	9.6 ± 0.3*†			
P_{aCO_2} (kPa)	Young	5.3 ± 0.1	5.6 ± 0.1	5.6 ± 0.1	5.1 ± 0.1	4.4 ± 0.2	<0.01	<0.01	0.95
	Old	4.9 ± 0.2	5.1 ± 0.2	5.0 ± 0.1	4.7 ± 0.1	4.0 ± 0.2			
P_{aO_2} (kPa)	Young	13.6 ± 0.1	12.8 ± 0.1	12.1 ± 0.2	12.6 ± 0.5	12.7 ± 0.4	0.99	<0.01	0.35
	Old	13.1 ± 0.4	12.6 ± 0.3	12.5 ± 0.4	12.3 ± 0.2	13.0 ± 0.2			
P_{vO_2} (kPa)	Young	4.8 ± 0.1	5.0 ± 0.1	5.0 ± 0.1	4.9 ± 0.1	5.0 ± 0.2	0.07	0.18	0.27
	Old	4.5 ± 0.2	4.6 ± 0.2	4.7 ± 0.2	4.7 ± 0.3	4.3 ± 0.2			
S_{aO_2} (%)	Young	98.4 ± 0.1	97.6 ± 0.3*	96.9 ± 0.2*	97.1 ± 0.3*	96.7 ± 0.3*	0.07	<0.01	0.02
	Old	98.1 ± 0.3	98.0 ± 0.2	97.8 ± 0.3	97.6 ± 0.2	97.8 ± 0.1†			
S_{capO_2} (%)	Young	81 ± 1	82 ± 1	82 ± 1	80 ± 1	78 ± 1	0.43	<0.01	0.99
	Old	80 ± 1	81 ± 2	81 ± 2	79 ± 1	77 ± 1			
P_{capO_2} (mmHg)	Young	44 ± 1	44 ± 1	44 ± 1	43 ± 1	41 ± 1	0.70	<0.01	0.99
	Old	43 ± 1	44 ± 2	44 ± 2	42 ± 1	40 ± 1			

Values are mean ± SEM. P values represent ANOVA results. *$P < 0.05$ *vs.* rest, †$P < 0.05$ *vs.* young.

limit exercise performance (Rasmussen *et al.* 2010). Notably, the administration of a β-adrenergic blocker (propranolol) concomitantly attenuates the increase in CO and cerebral perfusion during incremental exercise (Seifert *et al.* 2009*b*). At exhaustion ΔP_{mitoO_2} was reduced to a similar degree with or without β-adrenergic blockade, although with propranolol the absolute workload being performed was lower (Seifert *et al.* 2009*b*). In addition, ΔP_{mitoO_2} was similarly reduced during exhaustive exercise both before and after 3 months of endurance exercise training, despite the post-exercise workload being ∼20% greater (Seifert *et al.* 2009*a*). Rasmussen *et al.* (2010) reported that exhaustive cycling exercise and submaximal cycling in hypoxia, which both reduced ΔP_{mitoO_2}, elicited a reduction in the maximum voluntary contraction and voluntary activation of the elbow flexors (m. biceps brachii). As the resting twitch force produced by electrical stimulation of the elbow flexors was unchanged, it was concluded that the reduction in maximal force generation observed was central in origin. Thus, a mismatch between neuronal activity and O_2 delivery during exercise, and the accompanying drop in cerebral oxygenation and ΔP_{mitoO_2}, may lead to a suboptimal motor output and activation of exercising skeletal muscles (i.e. central fatigue) (Nielsen *et al.* 1999; Rasmussen *et al.* 2007, 2010; Seifert *et al.* 2009*b*). However, it should be acknowledged that at least in hypoxia, the augmentation of cerebral perfusion and oxygenation by CO_2 supplementation has no effect on exercise capacity (Siebenmann *et al.* 2012).

We observed a reduction in ΔP_{mitoO_2} by ∼5–10 mmHg during strenuous exercise (≥75% W_{max}) concomitant to reductions in OCI, and increases in RPE and fatigue (Rasmussen *et al.* 2007; Seifert *et al.* 2009*b*). Notably, the increases in $\Delta CMRO_2$ and reductions in S_{capO_2}, P_{capO_2} and ΔP_{mitoO_2} were similar during vigorous to maximal exercise in both young and older individuals, despite age-related reductions in cerebral perfusion. Therefore, as in young individuals with and without propanolol (Seifert *et al.* 2009*b*), the magnitude of the reduction in ΔP_{mitoO_2} in elderly individuals during exhaustive exercise (100% W_{max}) was similar to that established in the young subjects, although the absolute workload performed was ∼30% lower in the older group.

Limitations

Transcranial Doppler ultrasonography measures of MCA V_{mean} are only equal to those in CBF if the diameter of the MCA remains unchanged. Notably, MCA V_{mean} increases during dynamic exercise are paralleled by increases in CBF determined from duplex Doppler measures of ipsilateral internal carotid artery blood flow (Hellstrom *et al.* 1996), the 'initial slope index' of the ^{133}xenon clearance method (Jorgensen *et al.* 1992) and positron emission tomography evaluation of CBF (Poeppel *et al.* 2007). Furthermore, transcranial Doppler ultrasonography measures of MCA V_{mean} are used successfully in several reports examining the interactions between age, exercise and cerebral perfusion (Heckmann *et al.* 2003; Fisher *et al.* 2008; Marsden *et al.* 2012; Murrell *et al.* 2012). A greater MCA diameter in the older group may have meant we overestimated the age-related difference in cerebral perfusion (Rai *et al.* 2012), but the current data are consistent with studies using a range of imaging techniques (Kety, 1956;

Rogers *et al.* 1990; Ajmani *et al.* 2000; Scheel *et al.* 2000; Beason-Held *et al.* 2007; Ainslie *et al.* 2008). Further studies assessing the influence of age on the CBF responses to exercise using duplex Doppler assessments of the internal carotid and vertebral arteries (Hellstrom *et al.* 1996; Sato *et al.* 2011) would be valuable. Calculations of S_{capO_2}, P_{capO_2} and P_{mitoO_2} are based on arterial and internal jugular venous blood samples. Several assumptions and possible errors are implicit in the estimate of P_{mitoO_2}, and thus only changes from baseline are presented (Rasmussen *et al.* 2007; Seifert *et al.* 2009*a*). An alternative approach to assess CBF, oxygenation and metabolism may be with brain imaging techniques (e.g. functional magnetic resonance imaging); however, these techniques are unsuitable during high intensity dynamic exercise due to the high potential for motion artefacts. The absence of an assessment of plasma catecholamine concentrations is also a limitation of the present work.

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Author contributions

Experiments were performed at the Department of Anaesthesia, Rigshospitalet, University of Copenhagen, Denmark. The conception and design of the experiments was undertaken by J.P.F., J.J.vL. and N.H.S. Collection, analysis and interpretation of the data were undertaken by all authors. J.P.F. drafted the article and it was revised critically for important intellectual content by D.H., H.B.N., J.J.vL. and N.H.S. All authors approved the final version of the manuscript.

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Translational perspective

The present study sought to investigate cerebral perfusion, metabolism and oxygenation during exercise in aged humans. We observed that despite reductions in cerebral perfusion in older individuals during exercise at matched relative intensities, increases in brain uptake of oxygen, lactate and glucose occur to a similar extent in young and older individuals. Furthermore, the magnitude of the increases in the cerebral metabolic rate of O_2 ($\Delta CMRO_2$) and reductions in S_{capO_2}, P_{capO_2} and ΔP_{mitoO_2} were similar in young and older individuals, despite the absolute workload undertaken being lower in the older group. The extent to which these central changes represent a common element to exercise capacity (i.e. fatigue) requires further investigation.